Ethical Assessment of Clinical Asthma Trials Including Children Subjects

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ABSTRACT. *Background.* **The inclusion of children with asthma in clinical asthma trials is increasing, including their participation in placebo-controlled trials (PCTs). The objectives of this study are to assess whether children with asthma have been harmed by their participation in PCTs.**

Methods. **Seventy clinical asthma trials involving children published between January 1998 and December 2001 that involved distinct US research populations were identified. Studies were reviewed to determine whether all subjects with more than mild asthma received daily antiinflammatory medication as recommended by national guidelines. Sixty-two clinical asthma trials included data about subject withdrawal and were analyzed for the frequency of asthma exacerbations.**

Results. **Forty-five studies were designed as PCTs and did not require that all subjects with more than mild asthma receive antiinflammatory medications. Of 24 953 subjects, 4653 (19%) for whom data are available withdrew from research, and 1247 subjects (9.4%) withdrew from PCTs due to asthma exacerbations compared with 358 subjects (3.1%) in other trials. In PCTs, subjects withdrew more frequently from the placebo arms than the active-treatment arms and did so more frequently because of an asthma exacerbation (667 or 15% vs 580 or 6.5%). Fifty-two studies enrolled both children and adults, although only 1 performed subset analysis of the children.**

Conclusions. **Subjects enrolled in PCTs of asthma have been exposed to unnecessary risks and harms. Clinical asthma trials involving children and adults do not benefit children as a class because they rarely provide subset analysis of children subjects.** *Pediatrics* **2004;113: 87–94;** ***asthma, clinical trials, placebo-controlled trials, children, ethics.***

ABBREVIATIONS. NHLBI, National Heart, Lung, and Blood Institute; ICS, inhaled corticosteroids; PCT, placebo-controlled trial; IRB, Institutional Review Board; CAMP, Childhood Asthma Management Program.

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The opinions expressed in this article are those of the authors and do not reflect the opinions or policies of the National Human Genome Research Institute, the National Library of Medicine, the National Institutes of Health, or the Department of Health and Human Services.

Received for publication Dec 9, 2002; accepted Mar 14, 2003.

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Asthma is one of the most common chronic conditions of childhood.[1,2] In 1998, asthma affected nearly 4.5 million children in the US and resulted in >10 million missed school days,[3] 5.8 million outpatient visits, >867 000 emergency department visits, 174 000 hospitalizations, and >200 deaths.[4] The reduction of pediatric asthma morbidity is a national health care objective.[5,6] Research involving children is central to achieving this goal. The recent policy initiatives of the National Institutes of Health and the Food and Drug Administration[7–9] are attempts to increase the number of children enrolled in research and to permit their participation earlier in the drug-development process.

Despite a better understanding of the inflammatory pathogenesis of asthma and the development of clinical guidelines that recommend the use of antiinflammatory medications for children with asthma, a significant percentage of children with asthma remain undertreated.[10] The 1991 National Heart, Lung, and Blood Institute (NHLBI) *Guidelines for the Diagnosis and Management of Asthma*[11] recommend antiinflammatory medications for all children and adults with more than mild asthma. These guidelines were updated in 1997 to specify that any child or adult with mild persistent, moderate persistent, or severe asthma should receive inhaled corticosteroids (ICSs),[12] and these revisions were reaffirmed in 2002.[13]

However, although clinical research has been responsible for refinement of the clinical asthma guidelines, there have been recent observations that some subjects enrolled in clinical asthma trials may not be receiving standard therapy and may be harmed.[14,15] This is of particular concern in placebo-controlled trials (PCTs) in which patients do not receive antiinflammatory medications.[14,15] To date, however, there are no data to show how frequently this occurs or the extent to which such research includes children, who are a vulnerable research population.[16]

This study is a systematic review of the published literature to assess 1) how often children enrolled in clinical asthma trials receive antiinflammatory medications in accordance with NHLBI guidelines; 2) whether subjects, particularly children subjects, enrolled in PCTs are harmed more than subjects enrolled in other types of clinical asthma trials; 3) whether children enrolled in the placebo arms of PCTs are harmed more frequently than children enrolled in active-treatment arms; and 4) whether any generalizable knowledge about children as a class is reported by the studies that involve children and adults. We define a subject as being harmed by his or

her participation in research if he or she withdrew because of an asthma exacerbation. The harm of an asthma exacerbation may be short-lived and easily reversed (minor harm) or it may lead to hospitalization or even death (major harm). Both types of harm are amplified by the subjective experience of an asthma exacerbation for subjects and their families which ranges from mild to severe discomfort and may be associated with varying degrees of anxiety.

METHODS

A Medline search was performed to identify all clinical asthma trials that were published between January 1, 1998, and December 30, 2001. Articles were excluded if they 1) were conducted outside the US; 2) did not include subjects <18 years old; 5) did not include original data or involve active recruitment of subjects (eg, pooled analyses or meta-analyses); 6) were nontherapeutic (eg, pharmacokinetic studies or cost-benefit studies); or 7) focused on such related conditions as exercise-induced asthma, allergic rhinitis, or status asthmaticus. All articles were reviewed to ensure that each study represented a separate population or a distinct research methodology. Of the initial 450 articles, >200 (44%) were excluded as foreign studies. Seventy studies described in 76 articles (see Appendix) were included for further analysis.

The numbers of subjects who enrolled in, completed, and withdrew or were withdrawn from each clinical asthma trial was recorded. To account for subject withdrawals during active and placebo phases of crossover studies, each subject was counted once for every arm to which that subject belonged. The causes of withdrawals, including asthma exacerbations and adverse events, were recorded. We documented as asthma exacerbations all adverse events described as "worsening of asthma," "asthma exacerbation," "lack of efficacy," or "clinical exacerbation." Other measures such as decrease in forced expiratory volume in 1 second, nighttime awakenings, increased use of rescue medications, emergency department visits, and other symptom measures could have also served as evidence of asthma exacerbation, but they were excluded because of inconsistent reporting and variability of significance. Withdrawals caused by unspecified reasons or reasons specified as "other" often could only be determined in total, not for each treatment arm. Hospitalizations were recorded also.

The subjects' asthma severity and treatment before enrollment were recorded. Many studies prohibited concurrent use of any prescription or over-the-counter medication that might affect the course of asthma or its treatment. No inferences were made from these statements about what medications were prohibited, and we recorded only whether antiinflammatory medications were specifically allowed or prohibited.

Finally, we recorded whether all subjects with more than mild asthma in each study received antiinflammatory medications on enrollment and throughout the course of their participation in the research as delineated in the 1991 NHLBI guidelines.[11] If the study specifically referred to the 1997 NHLBI guidelines that distinguish mild intermittent from mild persistent asthma,[12] then we documented whether all subjects with more than mild intermittent asthma received antiinflammatory medications on enrollment and throughout the course of their participation in the research.

According to the 1991 NHLBI guidelines, ICSs are primary therapy for moderate and severe asthma in adults and for severe asthma in children.[11] In children with moderate asthma, the nonsteroidal antiinflammatory drug cromolyn was considered first-line therapy, and ICSs were to supplement or replace cromolyn if symptoms persisted.[11] Sustained-release theophylline was considered an alternative. In the 1997 NHLBI guidelines, ICS is primary therapy for mild persistent, moderate, and severe asthma in adults and children.[12] Sustained-release theophylline and cromolyn are considered alternatives to antiinflammatory medications. Leukotriene inhibitors may be considered an alternative, although "their position in therapy is not fully established."[12] Of note is that the 2002 NHLBI guidelines continue to recommend ICSs as primary therapy for children and adults with mild persistent, moderate and severe asthma.[13] Leukotriene inhibitors as well as sustained-release theophylline and cromolyn are now considered valid alternatives to antiinflammatory medications.[13] For the purposes of our study, we classified sustained-release theophylline, cromolyn, and leukotriene inhibitors as antiinflammatory medications to minimize the number of subjects classified as not receiving appropriate treatment. In contrast, long-acting β-2 agonists are considered complementary but not an alternative to ICSs in the 1997 and 2002 guidelines and are not included as antiinflammatory medications.[12,13]

We scored all articles using a data-collection worksheet formulated by us. To determine the validity of the worksheet, all 3 investigators independently reviewed and discussed ~10 articles until unanimity was achieved. Twenty other articles were coded by 2 investigators, 15 by M.J.C. and L.F.R. and 5 by M.J.C. and B.W. Differences were resolved through discussion, with eventual agreement on all classifications. M.J.C. then reviewed the remaining 40 articles independently, raising questions with L.F.R. and B.W. regarding 10 additional articles. Then L.F.R. randomly reviewed worksheet data on 20 of the 30 articles coded independently. There was full agreement. Three researchers were contacted to clarify data. Data were analyzed using Microsoft Excel for Windows. Statistical significance was calculated by χ^2 analysis.

University of Chicago's Institutional Review Board (IRB) approved the research and waived written consent for the 3 researchers contacted. The National Institutes of Health exempted the research from review.

RESULTS

The characteristics of the 70 eligible studies are given in Table 1. The average duration of trials, excluding the run-in period, was 26.8 weeks, ranging from 5 days to 6 years. All studies enrolled at least some subjects who would meet the criteria for daily antiinflammatory medications. Fifty (71%) studies used placebos, and most of them (n = 45) compared a drug against placebo (PCTs); the others (n = 5) were add-on trials in which all subjects continued on antiinflammatory medications.

Of the 45 studies that compared a drug against placebo, subjects in 6 (13%) were on appropriate therapy before enrollment. However, in all 6 of these studies, at least some subjects were taken off these medications during the trial. In none of the remaining 39 studies were all subjects who met the criteria for daily antiinflammatory medications begun on antiinflammatory medications after study enrollment, including the 11 trials in which only children subjects were enrolled.

The total number of studies enrolling only children was 18 (26%), 14 of which were PCTs. The percentage of studies that enrolled children and adults increased from just >50% in 1998 (8 of 15) to >70% in the remaining 3 years.

Of the 52 studies that involved both children and adults, only 2 included children <4 years old, and only 1 included subpopulation analysis of adverse effects according to age. Thirty-one of these studies were PCTs.

From the 70 studies, 29 688 subjects were available for analysis, including 218 subjects who were counted more than once because they were enrolled in 1 of 3 crossover studies. Our withdrawal analysis is based on the 62 studies (40 of which were PCTs) documenting withdrawals and involves 24 953 subjects.

Sixty-seven documented IRB approval, and 68 documented the procurement of informed consent.

Fig 1 describes NHLBI guideline adherence for all the subjects enrolled in the 70 studies. In only 18 (26%) studies were all subjects with more than mild asthma on antiinflammatory medications before the

TABLE 1. Study Characteristics

	Number
Trials eligible	70
Trials using placebos	50
Placebo as add-on versus experimental drug (add-on)	5
Placebo versus experimental drug (PCT)	45
After appropriate therapy prior to enrollment	6
PCTs	45
Trials involving children and adults	31
Trials involving only children	14
Trials involving children and adults	52
Trials differentiating between children and adults at baseline	8
Trials differentiating between children and adults in results	1
Average duration of trials in weeks (excluding run-in period)	
Mean	26.8
Median	12
Trials documenting withdrawal information	62
PCTs	40
Trials documenting source of funding	67
Pharmaceutical company	63
National Institutes of Health with pharmaceutical-sponsored medications	3
Academic institution	1
PCTs documenting source of funding	42
Pharmaceutical company	39
National Institutes of Health with pharmaceutical-sponsored medications	3
Academic institution	0
Trials documenting IRB review and approval	67
Trials documenting procurement of informed consent	68
Trials performed by year, no. (no. including only children)	
1998	15 (7)
1999	22 (4)
2000	20 (5)
2001	13 (2)
Subjects available for analysis (no. counted more than once)	29 688 (218)
Subjects enrolled in 62 trials documenting withdrawal information	24 953 (218)

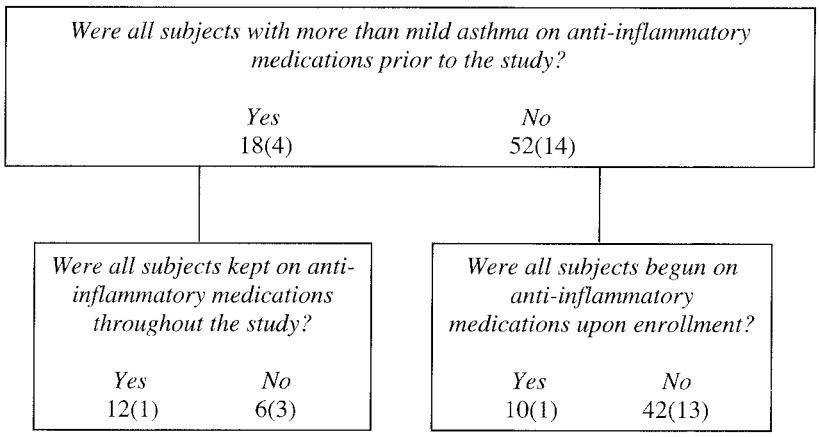

Fig 1. NHLBI asthma guideline adherence in clinical asthma trials including children (n = 70). Shown are the total number of trials with the number of trials including only children in parentheses.

study. In 6 (33%) of these studies, some of the subjects were taken off these medications during the trial. In the 52 studies in which all subjects were not on antiinflammatory medications before the study, only 10 (19%) were begun on appropriate treatment at the time of study enrollment. Only 1 of the 18 studies (6%) that enrolled only children subjects ensured that they received appropriate antiinflammatory medications after enrollment.

Asthma exacerbations account for ~33% of all withdrawals, slightly more if one only examines PCTs (44%; $P < .001$). Adverse events account for ~10% of all withdrawals, and the remainder of the withdrawals was due to other reasons (eg, noncompliance, protocol violations, failure to return for follow-up, etc) or not discussed (10%). Very few articles mentioned whether subjects were hospitalized, and it is not clear whether the information was not reported or whether subjects were only hospitalized in those studies that reported hospitalizations.

Table 2 shows the number of subjects who withdrew because of asthma exacerbations and the number who withdrew for all reasons in all studies for which those data are provided (n = 62). The first column shows the number of subject withdrawals and hospitalizations; 1605 (6.4%) subjects withdrew

TABLE 2. Subject Withdrawal

	All Trials (n = 62)	Add-On and Active-Controlled Trials (n = 22)	PCTs (n = 40)
Subjects analyzed, no.	24 953	11 690	13 263
Withdrawn because of asthma exacerbation, no. (%)	1605 (6.4)	358 (3.1)	1247 (9.2)*
Total Withdrawn, no. (%)	4653 (19)	1849 (16)	2804 (21)*
Hospitalized, no. (%)	122 (<1)	108 (<1)	14 (<1)

* Significant difference between PCTs and all other trials ($P < .001$).

or were withdrawn from research participation because of asthma exacerbation, accounting for 34% of all withdrawals. The second and third columns compare the withdrawal number for subjects in add-on and active-controlled trials (column 2) versus subjects in PCTs (column 3). The results show that subjects in PCTs withdrew or were withdrawn more frequently because of asthma exacerbations than subjects in add-on and active-controlled studies (1247 of 13 263 or 9.4% vs 358 of 11 690 or 3.1%; $P < .001$) and that subjects in PCTs withdrew or were withdrawn more frequently for all reasons than subjects in add-on and active-controlled studies ($P < .001$). Very few studies reported hospitalizations, accounting for <1% of all subjects.

Table 3 shows the number of subjects who withdrew because of asthma exacerbations and the number who withdrew for all reasons in the 40 PCTs for which withdrawal data are given, with a separate analysis for the 12 PCTs that include only children subjects in which withdrawal data are given. One thousand two hundred forty-seven (9.2%) subjects withdrew or were withdrawn from PCTs because of asthma exacerbations. One cannot determine from the available data whether adults or children withdrew, because none of the PCTs distinguished between children and adults in withdrawal data. Four hundred thirty-one (11%) subjects withdrew because of asthma exacerbations in studies that only included children. The total number of withdrawals for all reasons (row 3) includes 172 and 64 subjects (from 4 studies, 3 of which only enrolled children) who withdrew from unspecified study arms in columns 1 and 4, respectively, and are not analyzed further. Columns 2 and 3 specify the number of subjects who withdrew from active and placebo arms, respectively. The results show that subjects withdrew more frequently because of an asthma exacerbation from placebo arms ($P < .001$) and that subjects in the placebo arm were more likely to withdraw or be withdrawn for all reasons ($P < .001$). These differences were also found in PCTs that included only children subjects, as described in columns 5 and 6. Overall, children in placebo arms of PCTs involving only children were over twice as likely to withdraw because of asthma exacerbations as children in active-treatment arms (205 of 1180 or 17.4% vs 226 of 2906 or 7.8%; $P < .001$). The children in the placebo arm were also more likely to withdraw or be withdrawn for all reasons ($P < .001$). Few studies reported hospitalizations, and those that did failed to specify whether the subjects were children or adults except for one child hospitalized from the active-treatment arm of a PCT involving only children.

DISCUSSION

Our data show that, in 48 of 70 studies (69%), not all individuals who met criteria for daily antiinflammatory medications were treated in conformity with current NHLBI guidelines. In 6 studies, some subjects who had been on appropriate antiinflammatory medications were withdrawn from these medications. All these subjects were removed from appropriate antiinflammatory medications to enroll in a PCT studying an ICS. In only 10 of the 52 studies in which subjects were not on appropriate antiinflammatory medications before enrollment were all subjects begun and continued on appropriate antiinflammatory medications.

Virtually all the studies recorded IRB approval, meaning that they were scrutinized for their research ethics. However, according to the 1964 Declaration of Helsinki, an international code of research ethics, "in any medical study, every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method."[17] Clearly, then, the 48 (69%) studies that do not ensure that all the subjects who required antiinflammatory medications were receiving them in all study arms fail to achieve this goal. The revisions to the Declaration of Helsinki in 2000 are even more stringent, specifically rejecting PCTs where a standard of care exists.[17] Despite this, we found that none of the 45 PCTs ensured that all subjects who required antiin-

TABLE 3. Subject Withdrawal in PCTs

Study Arms	All Trials (n = 40)			Trials Including Only Children (n = 12)		
	All Arms	Active-Treatment Arms	Placebo Arm	All Arms	Active-Treatment Arms	Placebo Arm
Subjects analyzed, no.	13 263	8867	4396	4086	2906	1180
Asthma exacerbations	1247 (9.2)	580 (6.5)	667 (15)*	431 (11)	226 (7.8)	205 (17)*
Withdrawn, no. (%)	2804 (21)	1422 (16)	1210 (28)*	810 (20)	428 (15)	318 (27)*
Hospitalized, no. (%)	14 (<1)	9 (<1)	5 (<1)	1 (<1)	1 (<1)	0 (0)

* Significant difference between placebo arm and active arms ($P < .001$).

flammatory medications were receiving this medication.

A clarification to the Declaration of Helsinki in September 2002 permits the use of placebos when there are 1) "compelling and scientifically sound methodological reasons" and 2) a "therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm."[18]

It is not clear that there is a compelling and scientifically sound methodological reason to use PCTs for asthma research. In 2002, Miller and Schorr[19] questioned the scientific and ethical value of a "typical" pharmaceutically funded asthma trial because such studies typically compared an ICS against placebo. They argued that such studies lack scientific necessity because the value of ICSs has been well-established,[19] a concern that Miller and Shorr[14] elaborate on elsewhere. The methodological concern is that the studies lack equipoise.[20] In fact, in one of the studies we examined, the researchers explained: "Asthma symptoms would be expected to worsen in the placebo group during the treatment period because these patients were dependent on inhaled steroids but were not allowed treatment with inhaled steroids while in the study."[21] Our study also confirms the concern of Miller and Shorr[19] about pharmaceutically funded trials: of the 30 clinical asthma trials comparing antiinflammatory medications against placebo that mention funding, 27 were exclusively pharmaceutically funded.

PCTs of new antiinflammatory medications also fail to meet the second Helsinki requirement that permits placebos in the investigation of a "minor condition" provided that "the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm."[18] First, the reduction of pediatric asthma morbidity is a national health care objective[5,6] precisely because it is not a "minor condition." The avoidance of asthma exacerbations is a primary objective in clinical asthma management because an asthma exacerbation places the patient at risk of serious harm. Our data show that in PCTs, subjects on placebos are withdrawn because of asthma exacerbations significantly more often than children in active-treatment arms. One hundred twenty-two hospitalizations (0.4% of the subjects enrolled) and 3 deaths (none judged to be drug-related) were recorded, suggesting that most of the harm was not "serious," although many articles did not actually state what was required to alleviate the exacerbations. However, the second Helsinki requirement is not that the subjects should not experience serious harm, only that they be exposed to no additional risk of serious harm. And our data show that subjects with more than mild intermittent asthma who received a placebo instead of an antiinflammatory medication were placed at additional risk of serious harm.

Our data show a trend of increasing participation of children in studies that previously enrolled only adults. One explanation is recent policy initiatives.[7–9] Although these policies have succeeded in increasing the percentage of clinical asthma trials that enroll children, studies fail to show whether the therapies are safe and effective in children, the true goal of these initiatives. Of the 52 studies enrolling children and adults, only one performed subset analyses. As such, it was not possible to determine whether children enrolled in placebo or active-treatment arms of PCTs that included children and adults experienced benefits and risks in any way different from those experienced by adults. Some studies enrolled a significant number of children, suggesting that subpopulation analysis might have been possible. However, one cannot determine whether subpopulation analysis would have been possible in the 44 (85%) studies that included both children and adults but did not characterize subjects by age. Children are being exposed to the risks and harms of research, but there is no advance in pediatric medicine from their participation.

One limitation of our study was that we chose to only include US studies, although many clinical asthma trials are performed elsewhere. Those studies were excluded in part because different countries may hold research to different standards and in part because one of our goals was to examine the impact of recent policy initiatives on the inclusion of children.

A second limitation was that data from 8 studies were not included in our withdrawal analysis, including the Childhood Asthma Management Program (CAMP).[22] CAMP data could not be included, because the total number of withdrawals, exacerbations, and hospitalizations for each study arm and severity of asthma have not been reported yet in a way that would permit their inclusion. The researchers are currently analyzing the data and were previously not in a position to share their raw data (M.J.C., personal e-mail communication, March 2002). CAMP enrolled 1041 children who represent ~3% of the total number of subjects enrolled in all clinical asthma trials.

A third limitation is that all asthma exacerbations are grouped together. Ideally, we would be able to distinguish between increased symptomatology, increased use of rescue medications, the need for oral steroids, and/or emergency department visits. Such data were rarely available.

CONCLUSIONS

Current methodologies in many clinical asthma trials involving children are flawed despite IRB review. To conform to research ethics standards, all subjects who meet the criteria for daily antiinflammatory medications should receive ICSs or one of their alternatives in all arms of clinical asthma trials. Researchers, sponsors, and IRBs need to reevaluate how clinical asthma trials should proceed in the 21st century.

ACKNOWLEDGMENTS

Dr Ross' research on "children in research" is funded by National Institutes of Health grant NLM 1 G13 LM07472-01.

We thank Carol Stocking for invaluable advice and support.

APPENDIX

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"As I get older and forget more and more names, I'm finding it easier and easier to be compliant with HIPAA."

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